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Translational Control by the Eukaryotic Ribosome

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The ribosome plays a universally conserved role in catalyzing protein synthesis. Kondrashov et al. (2011) now provide evidence that the loss of function of ribosomal protein L38 in mice leads to a selective reduction in the translation of *Hox* mRNAs, thus suggesting that ribosomal proteins play a critical role during embryonic development.

In eukaryotes, during the initiation step of translation, 40S ribosomal subunits are recruited to the mRNA by proteins known as translation initiation factors (Sonenberg and Hinnebusch, 2009). The 40S ribosome complex with associated factors navigates the mRNA 5′ untranslated region (UTR) in search of the initiation codon. When the initiation codon is encountered, translation initiation factors are released and the 60S ribosomal subunit joins to form a translationally competent 80S ribosome. Translational control of gene expression is largely achieved via modulation of the activity of translation initiation factors, such as eukaryotic translation initiation factors 4E (eIF4E) and eIF2 (Sonenberg and Hinnebusch, 2009). These factors affect the translation of a subset of mRNAs, which harbor specific features in their 5′ UTRs. In contrast to eIFs, it is generally thought that ribosomes have a constitutive rather than regulatory role in mRNA translation (Stillman, 2001). However, in this issue, Kondrashov et al. (2011) provide evidence suggesting that the ribosome regulates gene expression during embryonic development by promoting the translation of a subset of mRNAs.

Ribosomal RNA (rRNA) serves as the catalytic core of the ribosome, whereas ribosomal proteins (RPs) are thought to facilitate optimal rRNA processing and folding (Stillman, 2001). Notwithstanding the differences in their composition and size, the constitutive role of the ribosome in catalyzing protein synthesis is conserved across all kingdoms of life (Stillman, 2001). Unexpected observations have emerged when studying human disorders collectively referred to as "ribosomopathies," in which genetic alterations occur in components of the ribosome machinery, including RPs. For instance, in Diamond-Blackfan anemia, mutations in several different RPs are associated with bone marrow failure and congenital birth defects leading to malformations in limb, face, heart, and kidney development (Ganapathi and Shimamura, 2008), thus suggesting that RPs play an important role during embryonic development.

Kondrashov et al. (2011) now show that mutations in RPL38 are responsible for developmental abnormalities displayed by the tail-short (*Ts*/+) mice, which exhibit skeletal patterning defects, including homeotic transformations, and compromised neural tube patterning. Surprisingly, *Ts*/+ embryos do not exhibit alterations in global translation as compared to wild-type littermates. However, the translation of a subset of mRNAs encoding Hox homeoproteins in embryonic tissues, including the neural tube and somites, is strongly reduced in Ts/+ embryos (Figure 1). Homeoproteins play an evolutionarily conserved role in controlling cell positioning and tissue patterning, which are the processes during which cells attain appropriate developmental fates (Gehring, 1987). Thus, these findings suggest that the ribosome plays a regulatory, rather than a constitutive role in modulation of gene expression during embryonic development.

Important issues concerning the mechanism by which RPL38 controls translation must now be addressed. A critical issue is whether RPL38 controls translation initiation of *Hox* mRNAs as an integral part of the ribosome or as an extraribosomal entity. The authors addressed this question by showing that in cytoplasmic extracts RPL38 is predominately found associated with ribosomes. In contrast, another ribosomal protein, RPL26, which binds to the 5′ UTR of *p53* mRNA and increases its translation in response to DNA damage, appears to function in an extraribosomal manner (Chen and Kastan, 2010). Thus, it is evident that future experiments will be required to address the question of ribosomal versus extraribosomal mechanisms of actions of ribosomal proteins in translational control.

Several other outstanding questions remain to be answered: Does RPL38 directly bind *cis*-regulatory elements in *Hox* mRNAs to control their translation? Do *trans*-acting factors (such as RNA-binding proteins or microRNAs) play a role in this process? And what can we expect in adult tissues? Significantly, individuals suffering from ribosomopathies

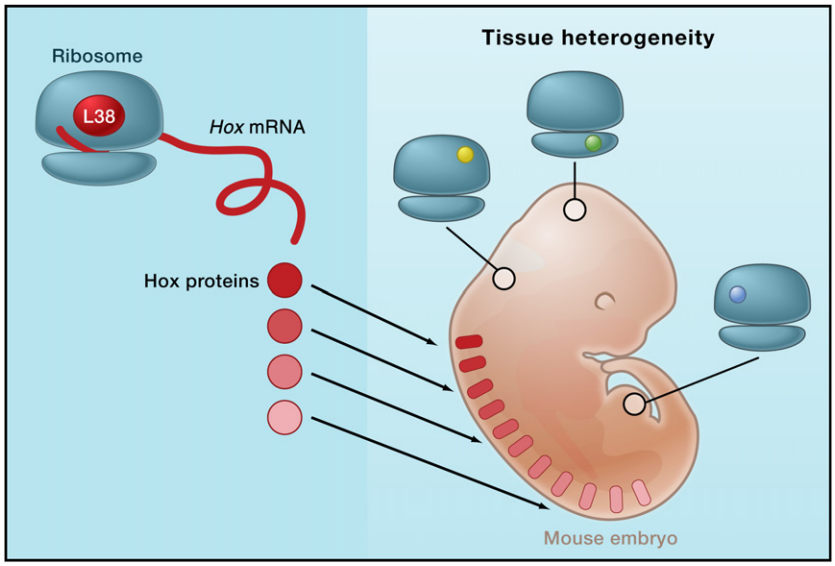

Figure 1. The Interface between Development and Translational Control
The loss of function of ribosomal protein RPL38 (L38) leads to a selective reduction in *Hox* mRNA translation. Reduced Hox proteins in the somites (red), which are precursors of vertebrae, leads to skeletal malformations characteristic of the Ts/+ phenotype. Tissue heterogeneity in the expression of ribosomal proteins (depicted in yellow, blue, and green) suggests that the changes in ribosome composition play an important role in the regulation of translation during embryonic development.

(such as Diamond-Blackfan anemia and X-linked dyskeratosis congenita) have increased predisposition to cancer (Ganapathi and Shimamura, 2008). The mechanisms underlying ribosomal dysfunction in cancer are still largely unknown, but the study of Kondrashov et al. raises the possibility that dysregulation of ribosomal function may lead to selective changes in translation that promote malignant transformation.

RPs are ubiquitously expressed and highly abundant (Stillman, 2001). Nonetheless, the authors report that RPL38 is enriched in developing tissues including eye, somites, and neural tube where aberrant tissue patterning is observed in Ts/+ mice (Kondrashov et al., 2011). This heterogeneity in the expression of RPs appears to be a general phenomenon during embryonic development, inasmuch as 72 RPs show inter-tissue variation in their expression levels. Previous findings in yeast by Komili et al. (2007) showing that RP paralogs appear to be functionally distinct gave rise to a provocative model of translational regulation wherein alterations in the composition of ribosomes lead to their "specialization" toward specific subsets of mRNAs (that is, a "ribosome code"). However, mammalian genomes, with a few exceptions, do not contain RP paralogs (Uechi et al., 2001). Although it is plausible that the differences in RP levels between tissues reflect their extraribosomal functions, tissue heterogeneity in the expression of individual RPs in the developing mouse embryo suggests that if a "ribosome code" exists in mammals, it may be established via modulation of RP expression.

Several key questions need to be answered to establish the existence of a "ribosome code." Molecular mechanisms that explain how the changes in the ribosomal composition and/or structure selectively affect translation of specific subsets of mRNAs are still elusive, and mRNA elements that correspond to "ribosome codes" are yet to be discovered. Given that both RPs and rRNA are extensively modified (Stillman, 2001), it is plausible that these modifications contribute to the "specialization" of the ribosome. Consistent with this notion, a key enzyme responsible for rRNA modifications is mutated in the X-linked dyskeratosis congenita syndrome resulting in selective impairment of translation (Yoon et al., 2006).

It is thought that the appearance of RPs in the ribosome predecessors of the RNA world accommodated the synthesis of longer polypeptide chains via stimulation of rRNA folding and improved efficacy and accuracy of mRNA translation (Fox, 2010). The findings of Kondrashov et al. (2011) raise the interesting possibility that some ribosomal proteins may have evolved to endow ribosomes with the capacity to modulate translation of specific mRNAs. The challenge posed by this intriguing study is to understand the mechanisms by which the ribosome controls translation in eukaryotes.

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